



A Meta-Selective Copper-Catalyzed C-H Bond Arylation

Phipps, R. J.; Gaunt, M. J. *Science* **2009**, 323, 1593

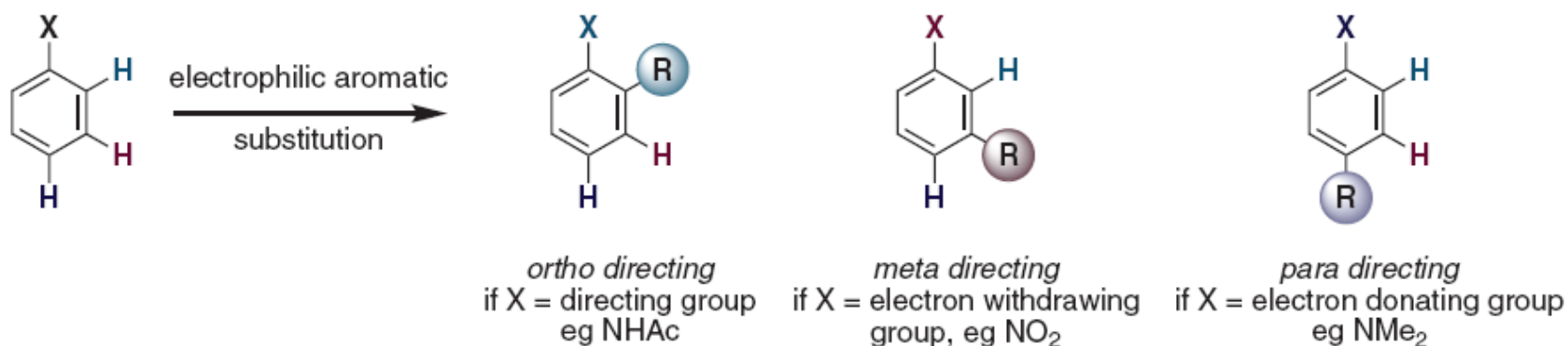
Nilanjana Majumdar
Literature Presentation
06.12.09

[Outline]

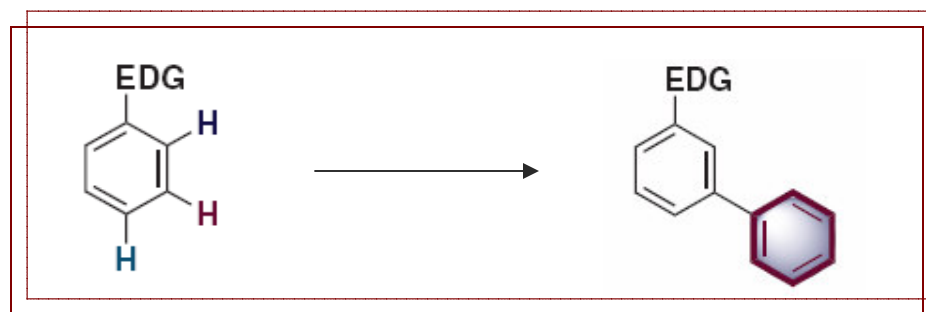
- Introduction
- Background (Previous Works)
- Present Paper
- Conclusion

Conventional Way & New Challenge

Conventional electrophilic aromatic substitution



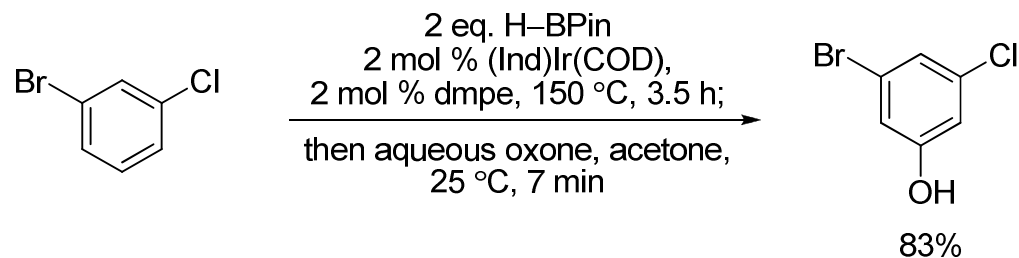
The Challenge:



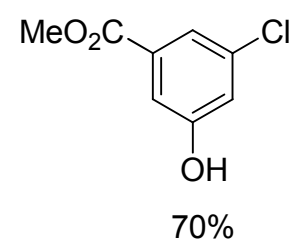
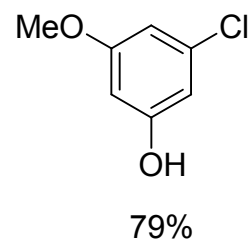
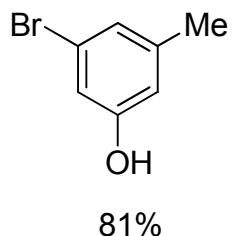
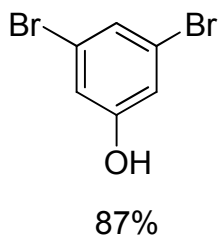
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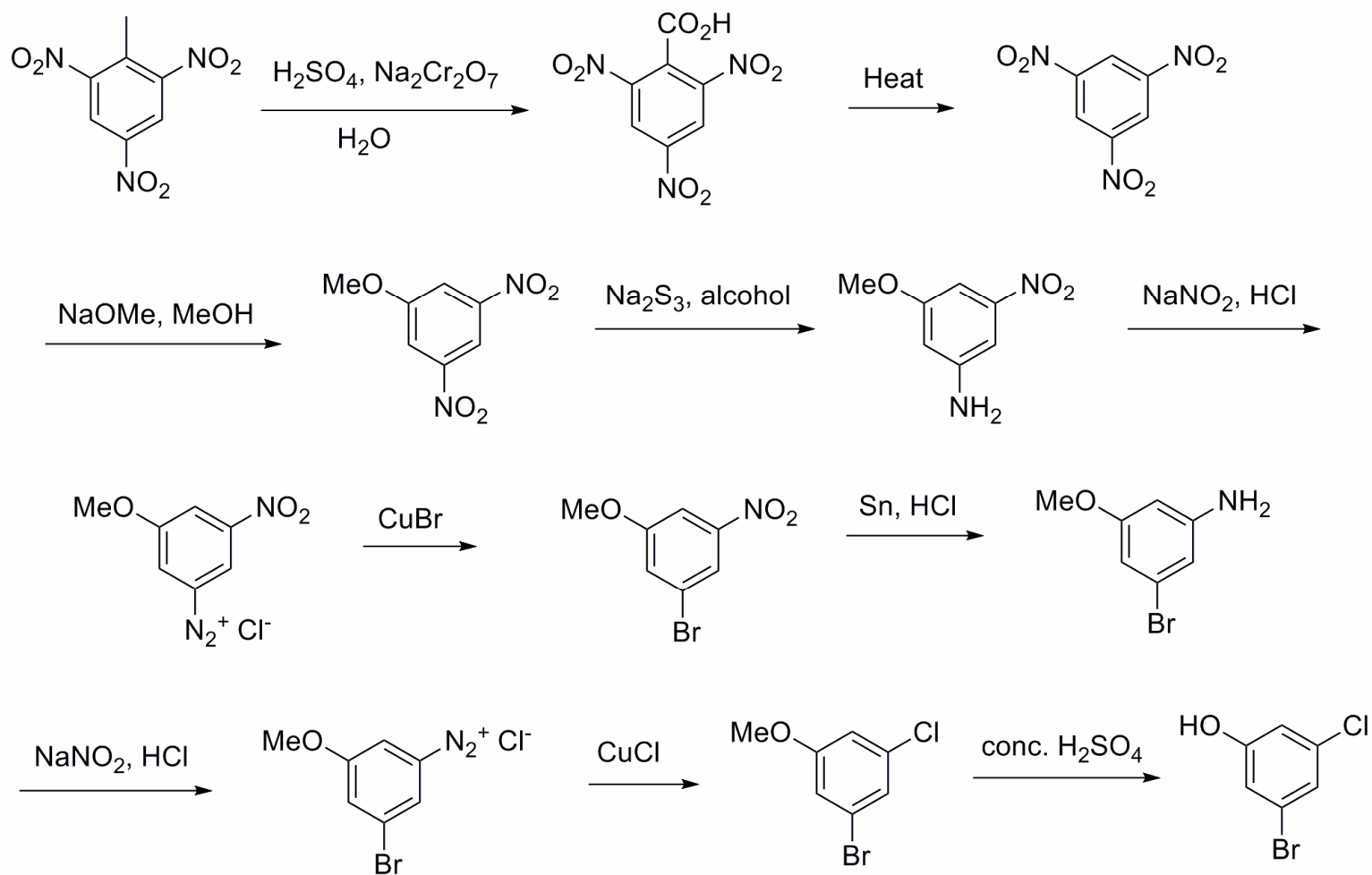
Maleczka-Smith Approach



10 steps from explosive TNT
in previous synthesis (1926)



Previous Synthesis

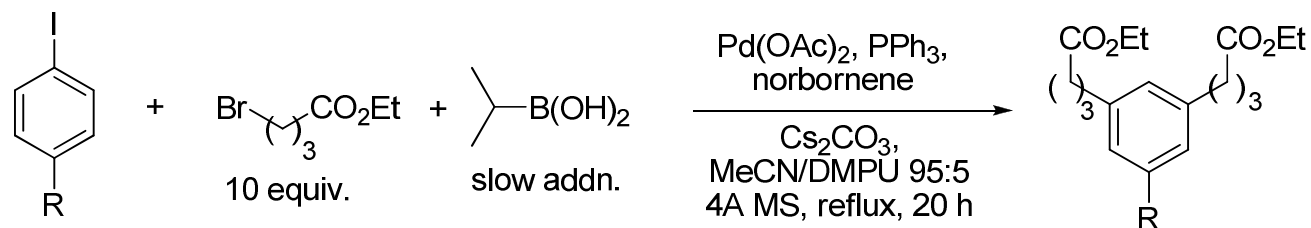


Hodgson, H. H.; Wignall, J. S. *J. Chem. Soc.* **1926**, 2077

Lautens Approach

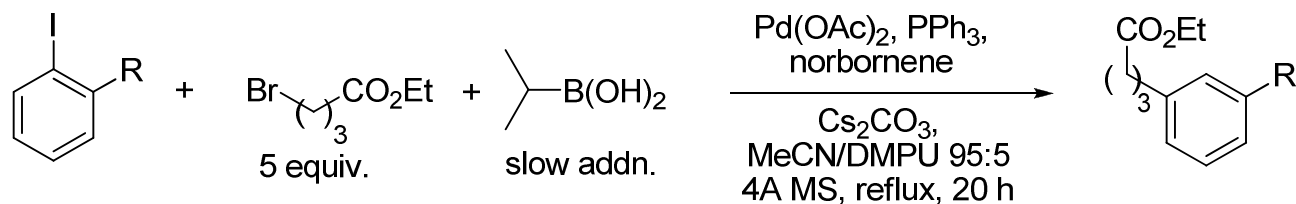
Scope of Ortho-Substituted Iodoarenes

Tri-Substituted Product:



R	Yield [%]
OMe	89
NMeTs	77
Me	60
Cl	68
F	64
OAc	40
CO ₂ Et	58
CF ₃	53
NO ₂	51

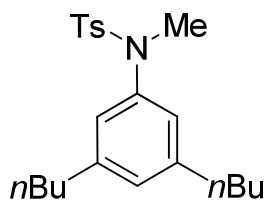
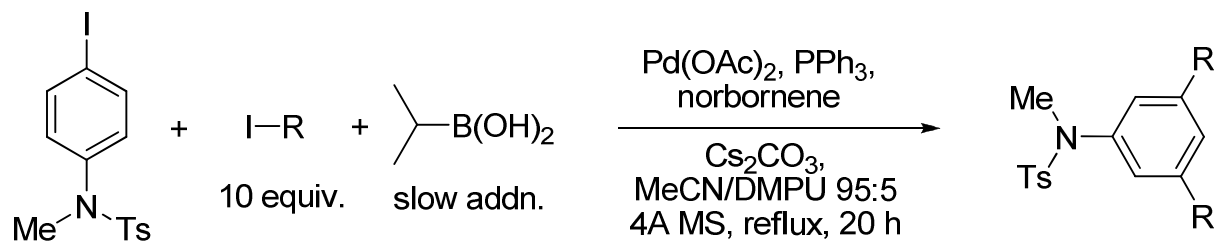
Di-substituted Product:



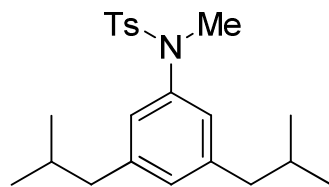
R	Yield [%]
OMe	36
NMeTs	71
Me	84
naphthyl	68
CF ₃	82
CH ₂ OTBS	89

Lautens Approach

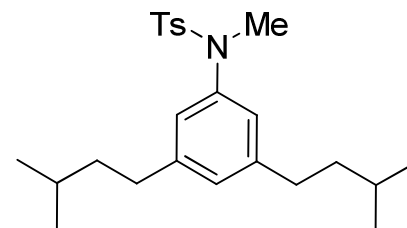
Scope of Alkyl Iodides



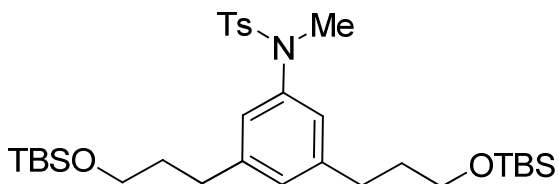
84%



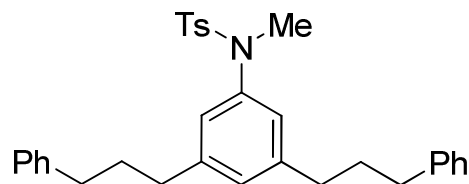
59%



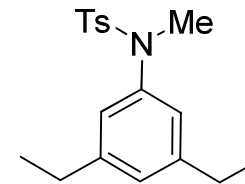
78%



77%

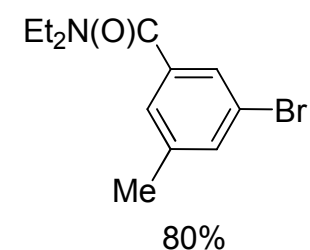
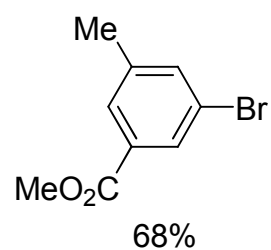
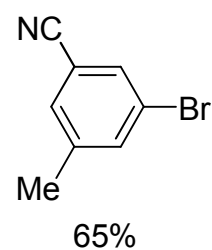
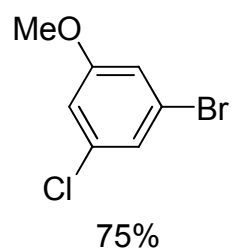
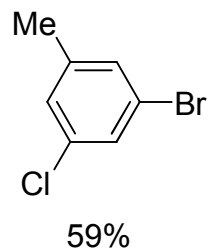
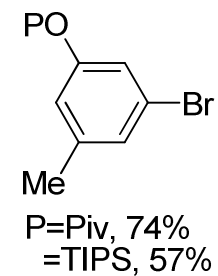
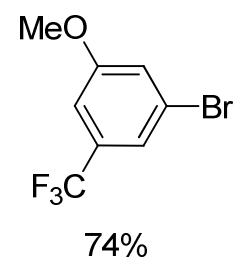
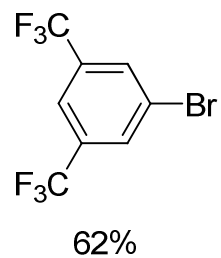
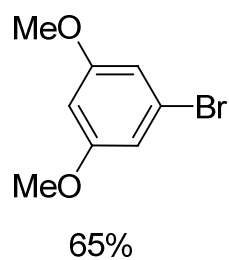
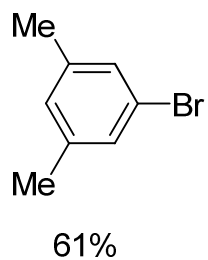
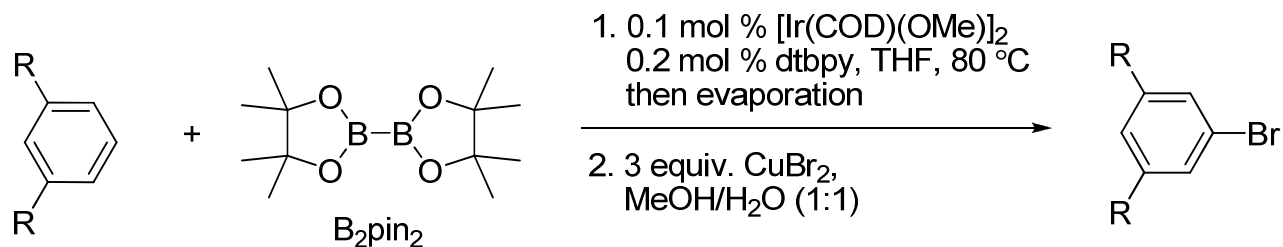


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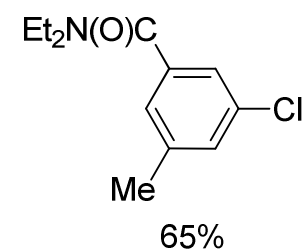
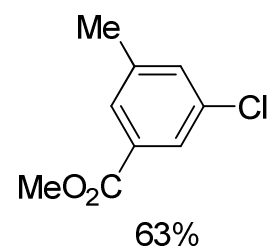
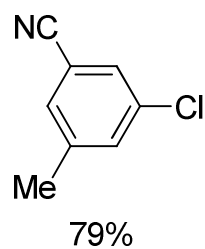
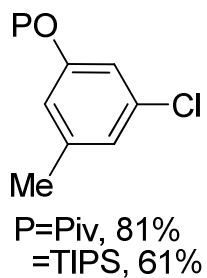
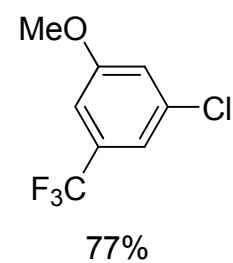
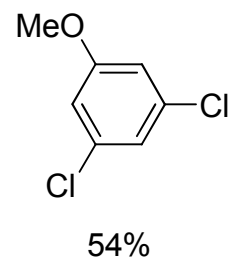
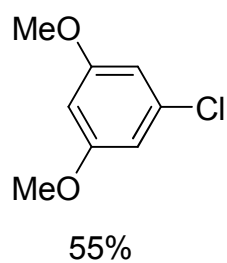
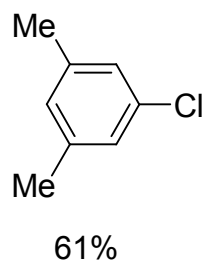
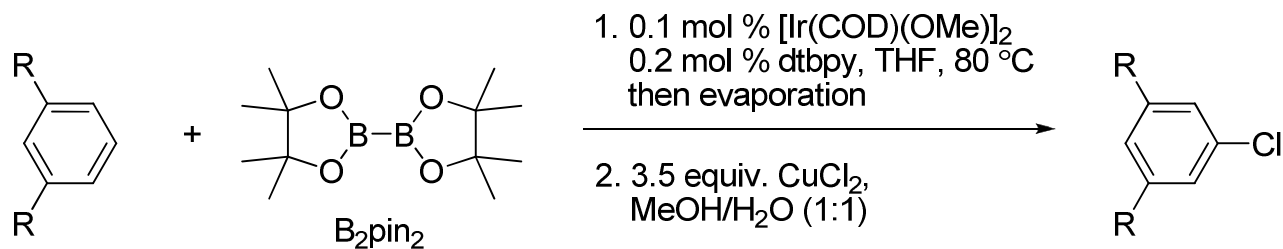


75%

Hartwig Approach



Hartwig Approach



[Drawback]

- These three approaches are three new directions in this field but there is limitation -

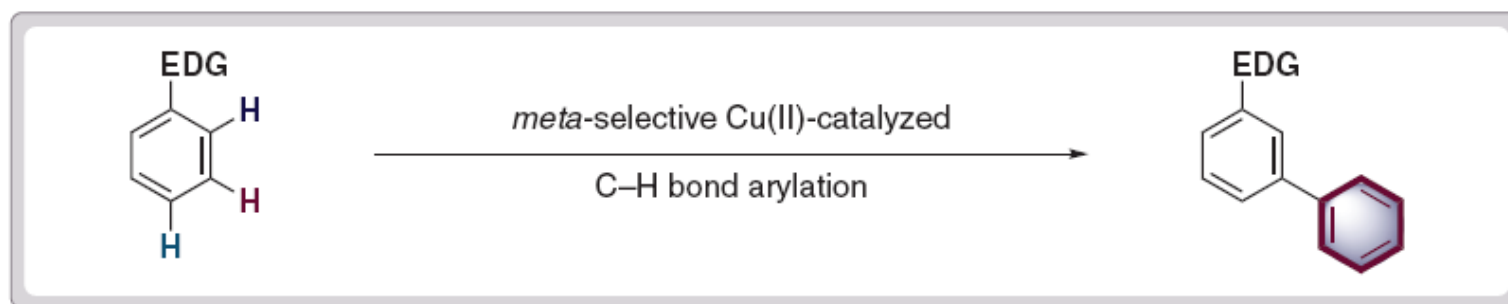
None of these methods can start with benzene bearing a single ortho/para donor and directly afford a single exclusive meta-substituted benzene.

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Gaunt Approach

Meta-selective catalytic C–H bond arylation



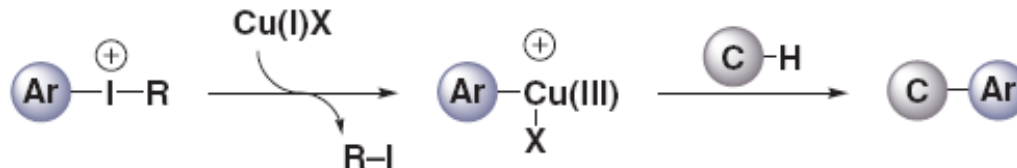
- Outcome not predicted by the conventional rules associated with electronic factors, directing groups, or steric effects.
- Provides direct access to the meta isomer.
- Process is simple, proceeds under mild conditions, uses inexpensive copper catalysts, and forms valuable products that would be difficult to synthesize by other methods.

Background

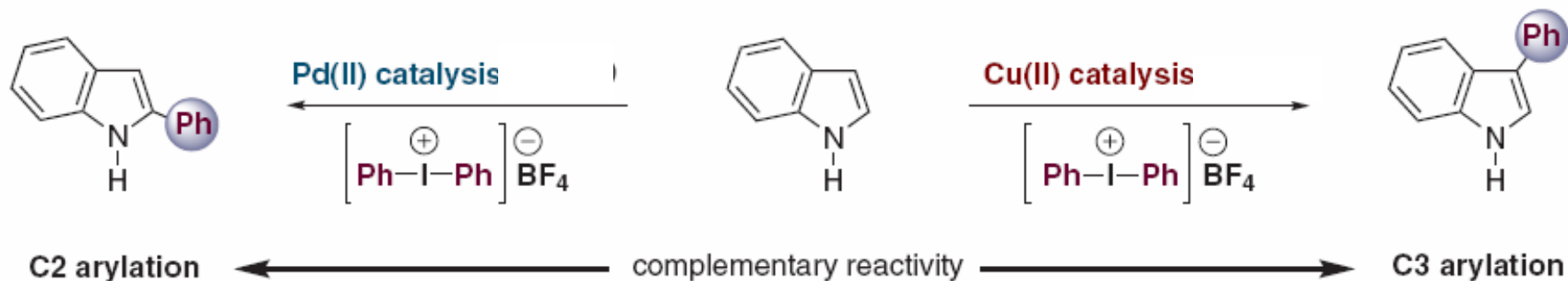
(A) Copper-catalyzed C–H bond functionalization concept

● Pd(II) is a d^8 metal
– electrophilic

● Cu(III) is a d^8 metal
– more electrophilic



(B) Complementary catalysis between Pd(II) and Cu(II)



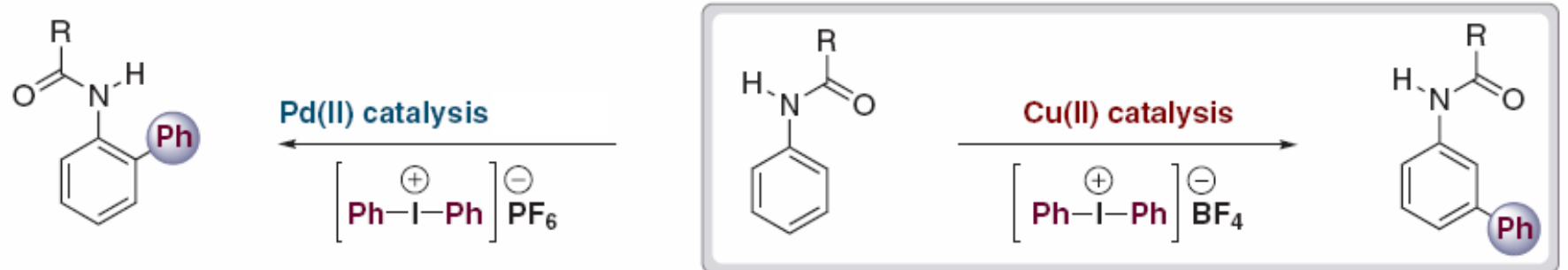
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Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, 128, 4972

Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, 130, 8172

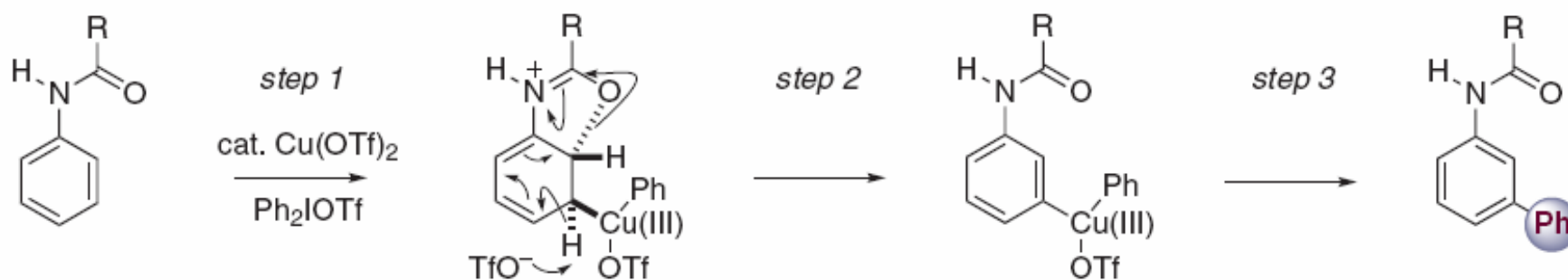
Reaction and Mechanism

(C) This study – *meta*-C–H arylation of acetanilides with Cu(II) catalysis



ortho-arylation ← complementary reactivity → *meta*-arylation

(D) Proposed mechanistic hypothesis



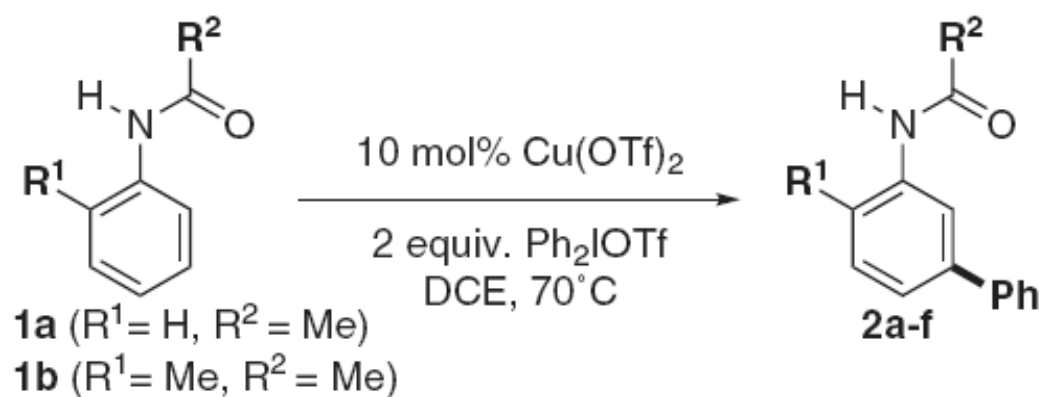
meta-C–H bond cupration via dearomatizing 'oxy-cupration'

Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, 44, 4046

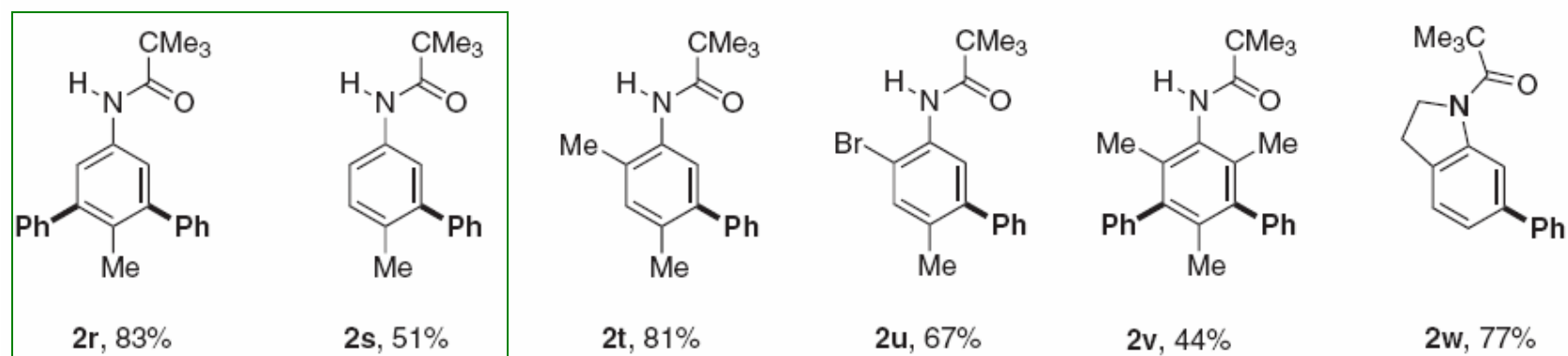
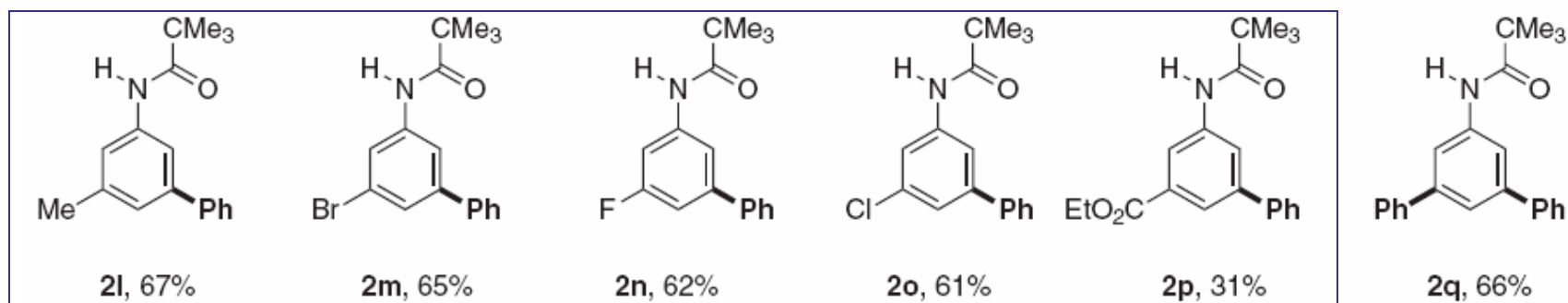
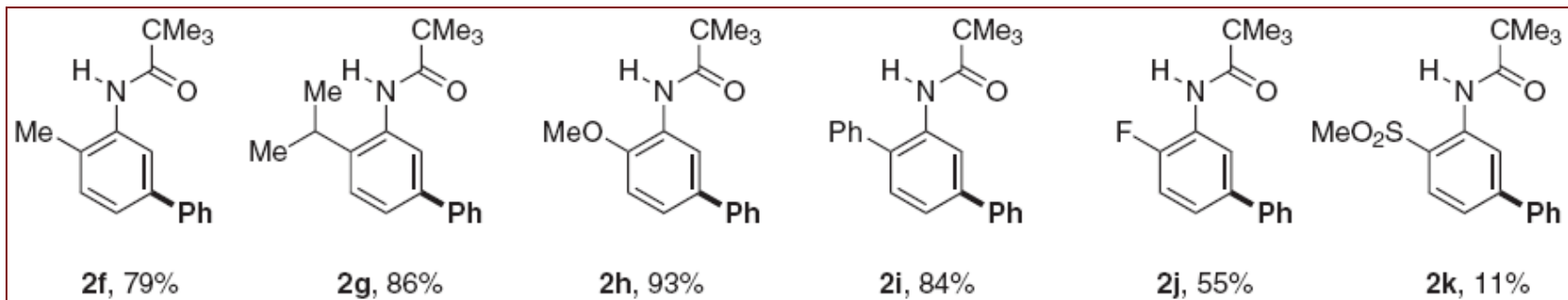
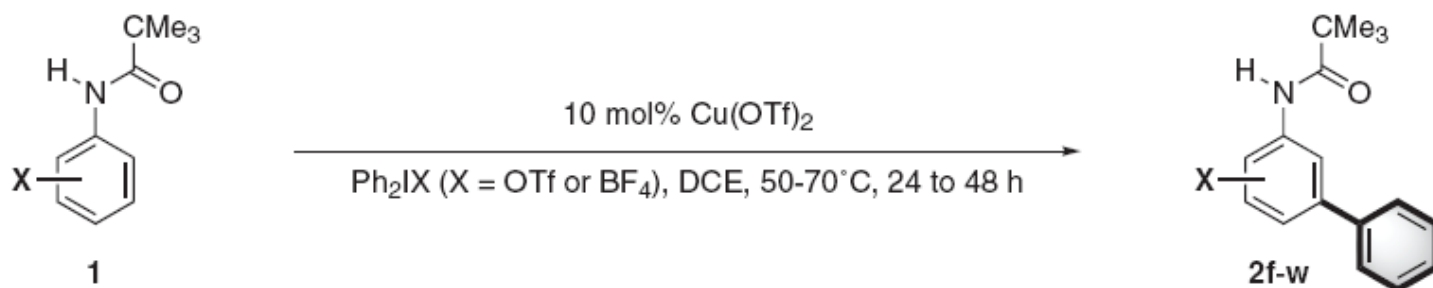
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Optimization

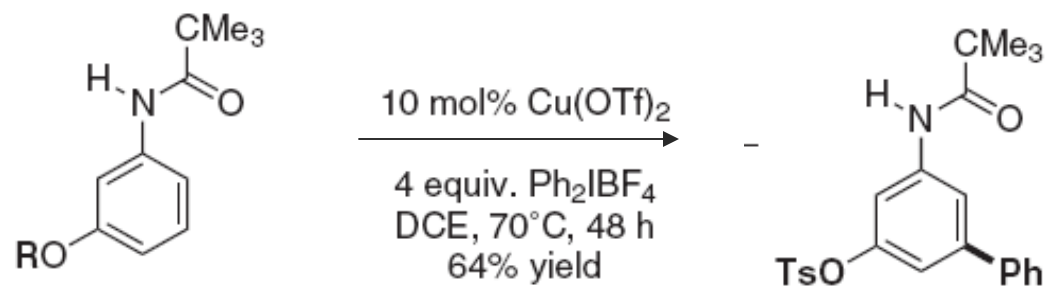
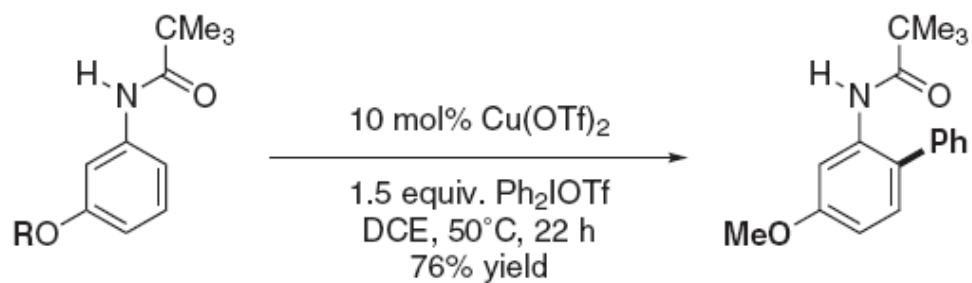
Reaction optimization



entry	R ¹	R ²	product	yield %
1	H	Me	2a	14
2	Me	Me	2b	43
3	Me	OMe	2c	45
4	Me	NEt ₂	2d	31
5	Me	Ph	2e	73
6	Me	CMe ₃	2f	79

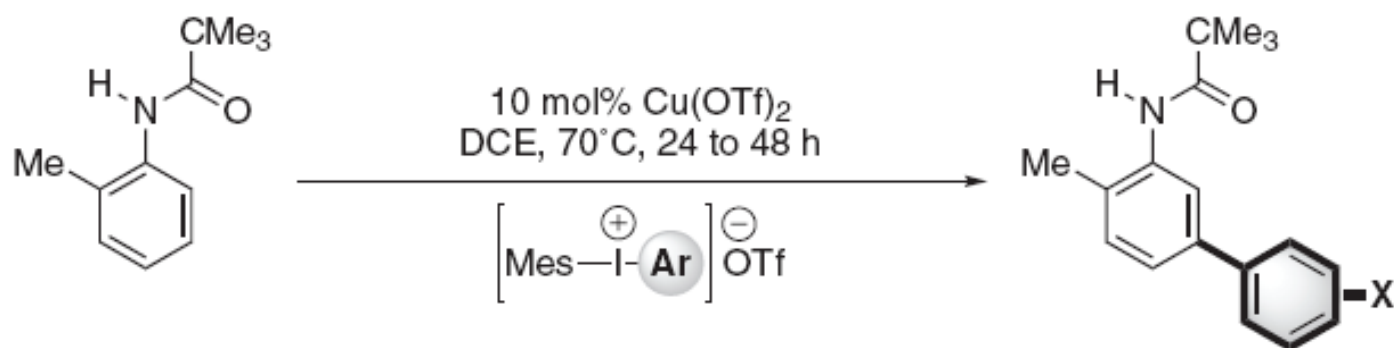


Controlling Regioselectivity



Variation of Aryl Substitution

Scope of aryl group transfer



X	yield
4-Me	82%
4-F	78%
4-I	49%
4-CO ₂ Et	82%
4-NO ₂	60%
3-CF ₃	70%
3-Br	72%
2-Me	44%

Conclusion

- Broad range of substrates is compatible with this operationally simple and mild copper-catalyzed arylation process.
- The method is best suited to more electron-donating substituents on the anilide ring, but still tolerates electron withdrawing groups.
- Amide group is a versatile motif that can be transformed into a range of other functionalities.
- Since organo-copper components need not be isolated, The reaction can be considered green.
- There are drawbacks to hypervalent iodides such as availability, by-product formation, and cost.

But still this reaction opens a new direction of light for this challenge

What besides aryl groups can be transferred?

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Maleczka, R. E. *Science* **2009**, *323*, 1572

